

## COMMENTARY

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## Comparative research on leukemia and related diseases: An introduction to a scientific approach

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XIX. SYMPOSIUM OF THE  
INTERNATIONAL ASSOCIATION  
FOR COMPARATIVE RESEARCH  
ON LEUKEMIA AND RELATED  
DISEASES

**Abstract** Publication in this journal of the abstracts of the Nineteenth Symposium of the International Association for Comparative Research on Leukemia and Related Diseases in Mannheim/Heidelberg led editor and publisher to suggest an article introducing comparative research in leukemia and related diseases. Our survey briefly summarizes the history of this symposium, as it evolved from a meeting on animal leukemia virus into one dealing with viral and genetic aspects of human and animal leukemia and related diseases. The scientific evolution of the Abelson murine leukemia virus with its *abl* oncogene in the 1970s to what currently appears as the most reliable marker for human chronic myeloid leukemia is merely one example.

**Key words** Comparative research · Leukemia · Retroviruses · Related diseases · Genome research

**Abbreviations** *HTLV* Human T-cell leukemia virus · *HIV* Human immunodeficiency virus · *SCID* Severe combined immunodeficiency

### Introduction

Comparative research has reached a new dimension with the recent advances in sequencing of the genomes of a variety of species and of humans. Many genes identified in the human genome and relevant for disease can be found in the genomes of animal species and even in the genomes of bacteria and of yeast. This reminds us that

not only human and animal biology but also pathology must be regarded as a continuum of evolution, and that much can be learned from comparing different species. Comparative research will allow conclusions to be drawn from principles recognized in animal species which are relevant to human diseases. It is likely that the application of comparative research to genome analysis will provide basic new insights in molecular medicine into the function of living beings for both animal species and humans. The current revolution in genomics is the latest phase in a rich history of medical progress related to the comparative approach.

### History

The principle of comparative research in cancer was recognized and first pursued systematically in the 1950s [1]. Similarities in morphology and biology between animal and human leukemias and related diseases and the recognition that leukemias in chickens and mice can be caused by viruses led to the concept that comparative research should promote the understanding of human leukemias and related diseases. In 1960, impressed by these morphological and etiological similarities, the World Health Organization inaugurated and sponsored the establishment of a World Committee for Comparative Leukemia Research. This committee was to promote cooperation and coordination of the study of leukemia in animals and humans on an interdisciplinary and international basis. One of the aims was to arrange international symposia every second year [1]. The first symposium took place in Hanover, Germany, in 1963, the 2nd in Stockholm, Sweden, in 1965, the 3rd in Paris, France, in 1967, and the 4th in Cherry Hill, New Jersey, USA, in 1969. After the 5th symposium in Padova, Italy, in 1971 the International Association for Comparative Research on Leukemia and Related Diseases was founded to com-

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**Table 1**

Species	Associated retrovirus
a) Vertebrates, in which leukemia or lymphoma is associated with a leukemia virus (selection)	
birds	Avian leukosis virus (ALV)
mice	Murine leukemia virus (MuLV)
cats	Feline leukemia virus (FeLV)
cattle	Bovine leukemia virus (BLV)
apes	Gibbon ape leukemia virus (GaLV)
man	Human T-cell leukemia/lymphoma virus (HTLV-I)
Neoplasia	Species
b) Other neoplasias, with which retroviruses are associated (selection)	
Sarcoma	birds
	mice
	cats
	rats
	monkeys
Mammary tumors	mice
Melanoma	fish

plement the World Committee and to expand the international effort.

### Retroviruses in leukemia and related diseases

The principal event for directing the attention of the scientific community to leukemia and for initiating comparative research on the disease in the search for a common etiology was the report by Gross in 1951 [2] that leukemia in mice can be transmitted by cell-free extracts. These experiments indicated that not only avian leukosis but also a mammalian leukemia can be caused by a virus. The observation by Gross was soon confirmed by others. In 1955 Graffi and coworkers [3] isolated a virus from spontaneous sarcoma filtrates which caused myeloid leukemia in mice. In 1957 Friend [4] obtained a filterable agent from a leukemic Swiss mouse which consistently produced erythroleukemia on serial transmission. In 1959 Lieberman and Kaplan [5] found leukemogenic activity in cell-free filtrates from radiation induced leukemias of mice. In 1960 Moloney [6] and in 1962 Rauscher [7] described viral agents that efficiently infect adult animals of most inbred strains of mice.

These reports in mice were extended to leukemias of other species such as cats and cattle in the late 1960s [8] and to apes in the early 1970s [9] (Table 1). Leukemias and subsequently immunosuppression in cats were shown to be caused by horizontally transmitted retroviruses [10, 11]. In 1969 the existence was confirmed in cell culture studies of a bovine leukemia lymphosarcoma virus which originally had been deduced from epidemiological observations in herds with bovine leukemia [12]. In 1972 a structurally and antigenically related virus was isolated from spontaneous lymphosarcomas and leukemias of gibbon apes (gibbon ape leukemia virus) [9]

which induces granulocytic and lymphatic leukemias in gibbons [13]. All these leukemia viruses are retroviruses.

During the 1960s and 1970s various retroviruses were found to be associated with solid-tissue fibrosarcomas in mice [14], cats [15], and monkeys [16]. All were reminiscent of the sarcomas of chickens described by Rous at the turn of the century, caused by "filterable agents" [17]. All were ultimately shown to be caused by cellular oncogenes transduced by retroviruses. Moving in and out of cellular DNA, retroviruses that replicated to the highest titers, for example, in cats and mice, gave rise to the largest number of distinct oncogenes. In 1970 Abelson and Rabstein described a defective leukemia virus that contained an oncogene, later termed *abl* [18].

Since most of the leukemia viruses are related to each other, the comparative approach led to a search for similar viruses or viral "footprints" in human leukemias. By electron microscopic and serological methods structures were observed in human leukemias and lymphomas that resemble retroviruses [19]. Most of these initial observations later proved to be false alarms. The "viruses" eluded isolation in culture or were shown to be contaminating rodent or monkey viruses. The identification of an RNA-dependent DNA polymerase (the reverse transcriptase) in retroviruses in 1970 [20, 21] provided a new tool for analyses of human leukemias, and reverse transcriptases [22] and nucleic acids related to animal retroviruses [23] were subsequently reported in a variety of human leukemias and cells. These approaches also failed to yield conclusive proof of a viral etiology for any human leukemia. Retrospectively, many of these observations were due to interference with endogenous retroviral sequences, with no specificity for the leukemic state [24].

A variety of hypotheses have been proposed from animal model systems to explain leukemogenesis by retroviruses, radiation, and/or chemicals (provirus theory, oncogene/virogene theory, provirus hypothesis, concept of promotor insertion by the insertion of regulatory viral sequences next to an oncogene etc.; for review see [25]). None of these theories, however, has proved really useful for a better understanding and management of human leukemias. The evolving evidence rather indicates that both leukemogenesis and carcinogenesis are multistep processes with several determinants, including environmental factors and genetic predisposition.

### Endogenous retroviruses

Endogenous retroviruses are inherited entities of normal cellular genomes. They can be induced from non-virus-producing cells with chemical and physical agents and were first identified in mouse and chicken cells [26, 27]. Comparative research led to the detection of endogenous retroviruses in virtually all vertebrate species that have been thoroughly examined, including rats, guinea pigs, deer, mink, cats, pigs, several primate species, and humans [24, 28, 29]. In most instances these viruses are

xenotropic because they grow best in cultured cells from other species. This is an important aspect in the ongoing public discussion on the risks of xenotransplantation in humans [30].

Genetically inherited retroviruses have been shown to be tumor inducing in a few instances (mink cell focus forming or MCF viruses, radiation leukemia virus, mouse mammary tumor virus, osteoma viruses) [5, 31–33]. However, such instances are apparently limited to highly inbred strains of rodents that were selected for the phenotype of leukemia, lymphoma, or mammary cancer [33]. Endogenous retroviral sequences can enhance the inherited tumor incidence of oncogene-transgenic animals. In humans they may disrupt genes, regulate tissue specificity of gene expression [34, 35], and be found in particles produced by human cells in culture [36].

In summary, comparative research on retroviruses has provided modern medicine with several new insights and methodologies of practical importance such as detection of reverse transcriptase, recognition of oncogenes and proto-oncogenes and identification of their biological functions (see below), isolation of a human leukemia virus (HTLV-I) and of the human immunodeficiency virus (HIV; see below), or development of retroviral vectors for gene therapeutic strategies.

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### Hematopoietic growth factors

In the 1970s the development of *in vitro* culture methods allowed the identification of a family of glycoprotein growth factors – the so-called colony-stimulating factors [37]. Prototype colony-stimulating factors were first purified and characterized in the mouse. The ability of these factors to control myeloid leukemic cell populations was established in mouse models such as WEHI-3B and R453 leukemias. Comparative studies with human and murine cells and leukemias also established the importance of colony-stimulating factors in human hematopoiesis. The subsequent identification [38] and recombinant production of human granulocyte colony-stimulating factors and other hematopoietic growth factors with their many applications in modern clinical hematology and in stem cell research can be considered the logical consequence of early comparative research [39].

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### HTLV-I

The identification and application of a lymphoid growth factor (T-cell growth factor or interleukin-2) [40, 41] finally allowed the identification of a human retrovirus and its association with a subgroup of human leukemias, the so-called human adult T-cell leukemia/lymphoma [42, 43]. The virus was designated as type I human T-cell leukemia virus (HTLV-I) because of its tropism for T-lymphocytes. The detection and characterization of HTLV-I ultimately was the consequence of the decade-long comparative search for a human leukemia virus and provided basic new insights into the biology of lympho-

cyte growth and biology. It also facilitated the later identification and characterization of HIV, which has a tropism for the same population of T-lymphocytes [44, 45].

Soon after the recognition of HTLV-I closely related retroviruses were found in African and Asian monkeys [46]. Designated as type I simian T-cell leukemia viruses, these retroviruses proved more complex than the gibbon ape leukemia virus mentioned above. The type I simian T-cell leukemia viruses have also been associated with leukemia development [47].

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### Neoplasms and retroviruses in poikilotherms

The comparative search for a common etiology of malignancies in different animal species associated various neoplasms (leukemia, melanoma) in poikilotherms, such as reptiles, fish, and even *Drosophila melanogaster* with developmental genes, inheritance, and retroviruses and viruslike particles [48–51]. These observations are in line with the recognition that species as well as their diseases must be considered as a continuous spectrum of evolution.

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### Oncogenes and proto-oncogenes

From the very beginning of the comparative approach in the 1950s the search for a viral etiology was not limited to leukemias and lymphomas but included related diseases such as breast cancer (or mammary tumors) [52] and sarcomas [53]. A filtrable agent transmitting avian sarcomas was detected in 1911 (Rous sarcoma virus) [17]. In the 1960s sarcoma viruses that transmit the disease were also detected in mice, rats, cats, and a woolley monkey [15, 16, 54, 55]. The specific feature of these viruses which distinguishes them from leukemia viruses is the presence in the viral genomes of cellular sequences which are responsible for the oncogenic properties (oncogenes) [56]. Almost identical sequences are present in normal cell genomes (proto-oncogenes) [57]. Comparative analyses demonstrated that proto-oncogenes exist in most species with high degrees of sequence similarities [58–63]. The oncogene, first detected in avian sarcomas, (*src* oncogene), for instance, has been detected in species

**Table 2** Selected neoplasias in animals and humans with which DNA viruses are associated (selection)

Neoplasia	Species	Associated virus
Renal adenocarcinomas	Frogs	Lucke herpesvirus
Lymphomas	Birds	Marek disease virus
Lymphomas	Monkeys	Herpesviruses saimiri and atele
Burkitt lymphoma	Humans	Epstein-Barr virus
Nasopharyngeal carcinoma	Humans	Epstein-Barr virus
Esophageal carcinoma	Cattle	Bovine papilloma virus
Carcinoma of the cervix	Humans	Human papilloma virus
Hepatocellular carcinoma	Woodchuck	Hepadnavirus
Hepatocellular carcinoma	Humans	Hepadnavirus (hepatitis B virus)

**Table 3** Human disease genes: comparative genomics

Gene	Gene product description	Chromosome localization	Animal homology	Associated diseases	Reference
MLH1	Gene product associated with DNA repair pathways in model organisms	3p21.3	Homology to yeast protein	Hereditary nonpolyposis colon cancer	114
Brcal	Human breast cancer locus 1	17q12-q21	Murine homologue	Mammary and ovarian carcinoma, prostate carcinoma	115, 116
CBFA2T1	Gene associated with acute myeloid leukemia		Murine homologue		117
RCK/P54	Gene derived from chromosomal translocation breakpoint region of a human lymphoma cell line, RC-K8	11q23	Murine homologue	Lymphoma	118, 119
Evi-2	Gene found between two neurofibroma translocations		Murine Evi-2	Recklinghausen neurofibromatosis	120, 121
NF1	Cytoplasmatic protein inhibits stimulatory RAS protein, NF1 encodes the protein neurofibromin, suggesting that NF1 plays a role in intracellular signaling pathways.		Avian model system	Neurofibromatosis type 1, also involved in juvenile chronic myeloid leukemia	122, 123
GBA	The defective enzyme is unable to metabolize glucocerebrosides which accumulate in characteristic distended phagocytic cells.	1q21	Gaucher mouse, targeted disruption of the glucocerebrosidase gene	Gaucher disease	124
AD3	Responsible for Alzheimer's disease in early-onset Alzheimer's disease families	14q24.3	<i>Coenorhabditis elegans</i> homologue	Alzheimer's disease, combined with the most severe form of the disease	125
MSH2	Homologous to an enzyme in the DNA mismatch repair pathway in bacteria	2p16	Bacteria	Gene mutated in some familial colon cancers	126
HD	HD protein with a molecular weight of 347000 (3144 amino acids) and CAG repeats encoding a segment of polyglutamine beginning 17 amino acids from the amino terminus. CAG repeat plays a critical role in the etiology of Huntington disease.	4p16.3	Mouse chromosome 5	Huntington disease	127
CFTR	Gene encoding a chloride channel protein, cystic fibrosis transmembrane conductance regulator, is responsible for adenosine 3',5'-cyclic monophosphate activated chloride transport in epithelial cells.	7q31	Mouse model for cystic fibrosis	Defective in patients with cystic fibrosis	128, 129
S-Leptin	Adipocyte-derived cytokine associated with regulation of body weight	7q31	Murine <i>ob</i> gene	<i>Ob</i> mutation in mouse is model system for studying human obesity	130
OAT	Ornithine aminotransferase	10q26	Murine homologue	Deficiency causing gyrate atrophy of the choroid and retina of the eye	131
PXR1	Gene product essential for peroxisome formation	12p13	PAS8, yeast homologue	Loss of PXR1 is associated with Zellweger syndrome	132–134
RB1	Tumor suppressor gene, a master control gene of cell cycle	13q14	Rat retinoblastoma antioncogene, 15q12	Inactivation causes retinoblastoma cancer of bone, bladder, small cell lung, and breast	135, 136
PKD1	Polycystin is an integral membrane glycoprotein involved in cell-cell/matrix interactions	16p13.2–13.3	Mouse model, tuberin gene ( <i>TSC2</i> )	Adult polycystic kidney disease	137, 138
P53	Tumor suppressor gene involved in triggering apoptosis protein can halt cell division	17p12-13	Mouse, leukemia in cattle	Deregulated proliferation, cancer	139, 140
DPC4	Tumor suppressor gene	18q21	<i>Drosophila</i> gene involved in transforming growth factor pathway	Loss causes aggressive pancreatic cancers	141, 142
LDLR	Gene encoding receptor for low-density lipoprotein	19p13.1–13.2	<i>Drosophila</i> , homologous gene is the vitellogenin receptor gene <i>yolkless (y)</i> , chicken, mouse	Naturally occurring mutations in humans cause familial hypercholesterolemia, heart disease	143, 144

**Table 3** (continued)

Gene	Gene product description	Chromosome localization	Animal homology	Associated diseases	Reference
ADA	Gene for adenosine deaminase	20q13.1	Mouse, yeast homologues	Deletion causing severe combined immunodeficiency	145, 146
SOD1	Gene coding for Cu/Zn superoxid dismutase	21q22	<i>Drosophila</i> gene as model homologue	Defect causes amyotrophic lateral sclerosis	147–151
ALD	Gene product involved in catabolism of long-chain fatty acids, adrenoleukodystrophy protein is an ATP-binding cassette transporter in the human peroxisome membrane	Xq28	PXA1 gene yeast	Defect causes adrenoleukodystrophy	152
DMD	Dystrophin gene	Xp21	Mouse model, mdx, a genetic homologue of human Duchenne muscular dystrophy gene	Defect causes Duchenne muscular dystrophy	153
PTC	Encodes transmembrane protein, tumor suppressor gene		<i>Drosophila</i> patched ( <i>ptc</i> ) gene	Defect causes basal cell nevus syndrome	154
APC	Tumor suppressor gene, cytoplasmatic protein	5q21-22	Rat model	Familial adenomatous polyposis coli, predisposition to colorectal cancers, stomach cancers	155, 156

as evolutionarily distant as *Drosophila* [64] and humans. Proto-oncogenes in many cases have later been identified as genes of growth-regulating factors or receptors for such factors in both animals and humans [65–70].

### Herpesviruses and lymphomas

Another field of intensive comparative research has been the association of members of the herpesvirus group with animal and human lymphomas such as Marek disease virus with chicken lymphomatosis [71], the herpesviruses saimiri [72], and ateles with lymphomas in monkeys and Epstein-Barr virus with Burkitt lymphomas [73, 74], nasopharyngeal carcinomas, and early Hodgkin's disease [75] in humans (Table 2). The regular association with Epstein-Barr virus has resulted in a serological test for nasopharyngeal carcinoma (Epstein-Barr virus viral capsid antigen IgA).

### Papilloma viruses, hepadnaviruses

Comparative analysis of similarities in bovine [76] and human papilloma viruses (Table 2) promoted the characterization of these viruses in men and their association with cervical neoplasia in women [77, 78]. This association may be of considerable practical relevance for prophylactic measures in the future.

Likewise, the woodchuck, duck, and ground squirrel hepatitis viruses served as useful models for research on hepatitis B virus and associated diseases, which include hepatocellular carcinoma [79]. These viruses, which are classified as hepadnaviruses, show features of and may be evolutionarily related to retroviruses (reverse transcriptase, RNA intermediate). Hepatitis B virus may induce hepato-

cellular injury. The resulting proliferative activity is thought to be important in hepatocellular carcinoma pathogenesis. Cytotoxic T-lymphocytes appear to be of central importance in this process by activating inflammatory cytokine release. Additional observations in the woodchuck system suggest that hepadnaviruses also make a more direct, genetic contribution to hepatocellular carcinoma. It therefore appears that several pathogenetic mechanisms may be operative in hepatocellular carcinoma in concert.

Comparative research on molecular biology and pathophysiology of hepadnaviruses in animal models has contributed considerably to the development of a vaccine against hepatitis B virus. Vaccination against hepatitis B virus has meanwhile been introduced in a worldwide effort to reduce the incidence of hepatocellular carcinoma.

### AIDS and immunodeficiency viruses

A more recent example for the success of the comparative approach stems from AIDS research. Immunodeficiency viruses have been identified not only in humans but also in animal species such as monkeys [80, 81], cats [82], and cattle [83]. The search for a retrovirus as a cause of human AIDS was based in part on the earlier knowledge that retroviruses cause immunosuppression in cats [84]. Due to their structural and biological properties, immunodeficiency viruses belong to the group of lentiviruses which cause various chronic diseases in animals, such as visna [85, 86] and maedi [87] in sheep, equine anemia [88, 89], and goat arthritis [90]. Studies of these animal diseases have provided insights into the transmission and biological behavior of lentiviruses, which in turn facilitated progress in research on human AIDS and HIV (pathogenesis, course of the disease, vaccination approaches).

The practical implications of comparative research on retroviruses in general and on immunodeficiency viruses for the management of HIV infection and AIDS are evident.

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### Comparative prion research

Another important area of comparative research is the area of prion diseases, an infectious disorder of protein configuration. Transmissible spongiform encephalopathy (scrapie) is observed in several animal species, such as sheep, goats, minks, mule, deer, and cattle ("mad cow disease"), and the disease has been transmitted to mice and hamsters in the laboratory [91–94]. All evidence indicates that human spongiform encephalopathies such as kuru [95], Creutzfeldt-Jakob disease [96], Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia follow the same pathogenetic pattern as the animal diseases [97, 98]. Transspecies infections between animals and from humans to monkeys are well known [95, 98].

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### Vaccines

The development of vaccines against retroviral diseases and other chronic diseases has been greatly facilitated by the comparative approach. Vaccines against feline retroviral diseases were in widespread use even before it was realized that a vaccine against AIDS would be needed [99]. Vaccines against Marek disease in chickens [100] also set a precedent for human herpesviral diseases, including Epstein-Barr virus associated nasopharyngeal carcinoma. Many of the principles in designing a human AIDS vaccine are currently being tested in the simian immunodeficiency virus model [101].

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### Transgenic mice, SCID mice

Advances in molecular biology and immunology have permitted the development of experimental animal models for comparative research. Functions of genes relevant for human pathology or development can be analyzed in transgenic animals [102], for example, through additional or altered genes, and deficiency "knockout" mutants for genes of interest. Pathogenic mechanisms of biological importance have been elucidated this way. It has been shown, for instance, that mice devoid of the prion protein (PrP) gene are resistant to prion disease, demonstrating that a normal host prion protein is essential for susceptibility to infection with prions [103, 104]. It has also been demonstrated that leukemia develops in mice transgenic for a rearranged human *BCR-ABL* gene, which is thought to be responsible for chronic myelogenous leukemia and for some acute lymphatic leukemias in humans [105].

The biological behavior of human cells and tumors and their accessibility to various drugs and treatments can be assessed in nude mice with severe combined im-

munodeficiency (SCID mice) [106, 107] which lack transplant rejection. Also, human blastic leukemias (acute and chronic myeloid leukemias) and lymphomas can be propagated in SCID mice [108–110]. The availability of these models greatly facilitates important aspects of biomedical, tumor biological, and genetic research.

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### Therapeutic progress in human leukemias

Therapeutic progress in human leukemias has been achieved principally by empiric approaches that make little use of the information obtained in the various fields described above. Comparative research contributes to the areas of hematopoietic growth factors (see above) and molecular surveillance such as the detection of the *BCR-ABL* rearrangement in chronic myelogenous leukemia or acute lymphatic leukemia.

New cytostatic drugs and the development of bone marrow transplantation provide the main tools for prolonging life and curing human leukemias. Nevertheless most recent symposia of the International Association for Comparative Research on Leukemia and Related Diseases have focused on therapeutic progress in acute and chronic leukemias in several sessions. Childhood acute lymphoblastic leukemia has become a curable disease in 70% of cases, and also cure rates of 30–40% are reported in adult cases of acute lymphatic leukemia [111, 112]. Myeloid leukemias are prognostically somewhat less favorable, but long-term survival rates of 25–35% have been observed in patients with acute myeloid leukemia who are aged below 60 years. In chronic myeloid leukemia about 60% of sufficiently young patients who have an HLA-compatible donor can be cured by allogeneous bone marrow transplantation. A significant prolongation of survival has been achieved by the introduction of interferon- $\alpha$  [113].

New therapeutic approaches address molecular and cytogenetic targets that may allow specific interventions such as the inhibition of the *BCR-ABL* specific tyrosine kinase in chronic myeloid leukemia or the use of all *trans*-retinoic acid in acute myeloid leukemia M3 with its translocation t(15; 17) at the site of the retinoic acid receptor.

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### Prospects of the comparative approach

An important prospect is comparative genome research relevant to human pathology. Table 3 summarizes 25 human disease genes for which animal correlates have been identified. Another prospect is a better characterization of human diseases with well-defined etiologies or pathophysiologies that can be compared to corresponding diseases in animals. Animal research is frequently carried out in inbred strains whereas the situation in humans is generally that of a wild-type population. The identification of carefully characterized subentities of human

disease, for instance, in geographically or genetically characterized subgroups, is therefore of special interest. Examples include the geographic clustering of human T-cell leukemias and lymphomas in southern Japan which are associated with HTLV-I, and the Epstein-Barr virus associated Burkitt lymphoma in eastern Africa. Also, ethnic differences in cancer predisposition or variations in cancer incidence depending on environmental influences and individual predisposition might provide clues. Epidemiological studies, combined with a careful nosology, would be helpful in this context. The comparative approach could complement and facilitate such epidemiological and nosological studies. The present symposium will therefore end with a session that deals with the epidemiology of human leukemia.

## Conclusions

Comparative research has been a highly successful scientific approach in research in leukemia and related diseases and in tumor biology in general during recent decades. It is likely that in the future this approach will continue to provide the basis for progress and insights in many fields of biomedicine in which similarities between animal and human diseases permit conclusions to be drawn from one species to solve questions in another. The past decade has shown that the value of the comparative approach is not limited to leukemia and related neoplasias but can also be applied successfully to nonneoplastic diseases such as AIDS and spongiform encephalopathies and to the analysis of basic biological questions in created animal models such as SCID mice and transgenics. The coming decade will see an unprecedented wealth of new biological information from genome sequencing in many species. The comparative approach is likely to continue to be indispensable to guaranteeing optimal use of available information for progress with human disease.

**Acknowledgements** We thank G. Pasternak, W. Seifarth and G. Papakonstantinou for literature search, the members of the World Committee (A. Burny, G. de The, E. Gluckman, L. Chieco-Bianchi, G. Saglio, G. de Boer, M. Dexter, V. Erfle, D. Hoelzer, M. Mulcahy, S. McCann) for encouragement and P. Duesberg for critically reading and commenting on the manuscript.

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